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State-of-the-Art: Hypo-responsiveness to oral antiplatelet therapy in patients with type 2 diabetes mellitus

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Abstract

Diabetes mellitus is a global pandemic, associated with a high burden of cardiovascular disease. There are multiple platelet derangements in patients with diabetes, and antiplatelet drugs remain the first-line agents for secondary prevention as well as for high-risk primary prevention among patients with diabetes. This review provides a summary of oral antiplatelet drug hypo-responsiveness in patients with diabetes, specifically aspirin and Clopidogrel resistance. Topics discussed include antiplatelet testing, definitions used to define hypo-response and resistance, its prevalence, association with clinical outcomes and strategies to mitigate resistance. The role of prasugrel and ticagrelor, as well as investigational agents, is also discussed.

Keywords

diabetes mellitus; antiplatelet resistance; high on-treatment platelet reactivity; aspirin resistance; Clopidogrel resistance; platelets; antiplatelet

Introduction

Diabetes mellitus is a rapidly expanding global pandemic, with nearly 400 million people worldwide having diagnosed diabetes mellitus.[1] Its prevalence worldwide is expected to double in the next decade. [2] An equal or likely higher number of people worldwide have

either undiagnosed diabetes or impaired fasting glucose. [3, 4] Coupled with a steep increase in childhood obesity and a proliferation of other risk factors such as excessive caloric intake and sedentary behaviors worldwide,[5, 6] it is one of the most important public health problems of our times. Indeed, it is estimated that 1 in 3 people born in the 21st century will develop diabetes mellitus during their lifetime. [7] In the United States, prevalence rates appear to have plateaued at ~8% between 2008 and 2012, but incidence rates continue to rise among minority populations. [8]

Diabetes is also one of the most important risk factors for the development of coronary atherosclerosis, including myocardial infarction (MI), [7, 9, 10] and is considered by some a CAD risk equivalent for the risk of future MI and cardiovascular death in adults age over 40 without known CAD.[11, 12] Among patients presenting with an acute coronary syndrome (ACS), patients with diabetes are more likely to have multivessel disease compared with patients without diabetes. [13] Furthermore, despite modern and appropriate dispensation of therapies for ACS,[14] the presence of diabetes mellitus continues to convey an adverse post-MI prognosis, making it one of the highest-risk subsets of patients presenting with ACS and representing a significant unmet clinical need toward closing the gap of the residual CVD risk associated with diabetes. [13, 15, 16] Toward this end, the development and application of more effective antiplatelet therapies remains a promising scientific front, especially for patients with diabetes.

The “angry” platelet in diabetes mellitus

Patients with diabetes have multiple platelet derangements that result in platelet hyper-reactivity and hyper-aggregability, resulting in so-called “angrier” platelets. [17] While the etiology of increased platelet activation is multifactorial and is discussed below (Figure 1), the consequences are higher rates of ischemic complications in those with diabetes mellitus. [17, 18]

Hyperglycemia

Chronic hyperglycemia is a causal factor for platelet hyper-reactivity and *in-vivo* platelet activation in patients with diabetes. [19, 20] Hyperglycemia promotes non-enzymatic glycation of platelet surface proteins, which decreases membrane fluidity and their propensity for activation.[21] Osmotic activation, protein kinase C activation, thromboxane overproduction and impaired calcium homeostasis in the platelets are all important mechanisms thought to increase increasing platelet aggregation. [22-25] Hyperglycemia is also associated with increased surface expression of glycoproteins Ib and IIb/IIIa, which are directly involved in platelet aggregation to other platelets and to leukocytes.[26]

Insulin resistance and insulin deficiency

Insulin inhibits the effect of platelet agonists such as collagen, ADP, epinephrine, and platelet-activating factor, primarily by activation of an inhibitory G protein by insulin receptor substrate (IRS)-1.[27, 28] Insulin also appears to inhibit the P2Y₁₂ pathway. [29] Thus, a relative or absolute lack of insulin can increase platelet reactivity. Insulin resistance, the more common situation in type 2 diabetes, adversely affects platelets via IRS-1

dependent and independent pathways. Insulin resistance causes an increase in intracellular calcium concentration that leads to augmented platelet degranulation and aggregation, an action mediated via IRS-1. [30] Recently, allelic variants of the IRS-1 gene have been shown to be associated with a hyper-reactive platelet phenotype in patients with type 2 diabetes.[31] IRS-1 independent pathways include decreased sensitivity to nitric oxide and prostacyclin. [32] Weight-loss engendered improvements in insulin sensitivity, as measured by homeostasis model assessment of insulin resistance (HOMA-IR), improved endothelial function and platelet function in a small but intriguing study.[33]

Oxidative stress, inflammation and endothelial dysfunction

Patients with diabetes have a pro-inflammatory milieu that appears to adversely affect platelet function in a number of ways.[34, 17] For one, reactive oxygen species increase the intraplatelet release of calcium following activation. They also limit the biological activity and response to endogenous nitric oxide and prostaglandin I₂. [35] These superoxides further activate protein kinase C and nuclear factor- κ B, with a resultant proliferation in genes promoting inflammation and thrombosis in endothelial cells.[36] Increased circulating fibrinogen levels also promote platelet hyper-reactivity in patients with diabetes.[37, 17] Intriguingly, inflammation may also increase the turnover of platelets. This can introduce un-inhibited and larger platelets into the circulatory pool in patients taking antiplatelet medications, and simultaneously increase the proportion of reticulated and micro-vesiculated platelets in the circulation, resulting in larger mean platelet volumes, thus expanding the net platelet surface area exposed for aggregation.[38, 39] Reticulated platelets also appear to be less responsive to antiplatelet therapy. [40]

Lipid abnormalities

Abnormalities of lipid metabolism are common in patients with diabetes, especially hypertriglyceridemia. Very-low-density lipoprotein (VLDL) that is rich in triglycerides increases platelet reactivity, partly through the effects of apolipoprotein E.[41]

Antiplatelet medications

Antiplatelet medications remain the cornerstone for the management of patients with both stable and unstable coronary artery disease.[42, 43] They prevent platelet adhesion, aggregation and activation thereby reducing risk for ACS events, stroke, and cardiovascular death.[44, 45] Currently available and commonly used oral antiplatelet medications include aspirin, Clopidogrel, prasugrel and ticagrelor. Others such as vorapaxar, ticlopidine and cilostazol are available, but infrequently used. Aspirin, or acetyl salicylic acid (ASA), exerts its antiplatelet action mainly by irreversibly acetylating a serine residue of platelet cyclooxygenase (COX)-1,[46] thus inhibiting the formation of thromboxane (TX) A₂, which is a potent stimulator of platelets. Clopidogrel and prasugrel are both thienopyridines, and exert their antiplatelet effects by irreversibly blocking the P2Y₁₂ receptor, thereby inhibiting platelet activation through ADP, and thus limit ADP-mediated conversion of glycoprotein IIb/IIIa to its active form. [47, 48] Both Clopidogrel and prasugrel are pro-drugs that require metabolic conversion to their active metabolites in the liver. [49] Prasugrel demonstrates less variability than Clopidogrel in antiplatelet efficacy, presumptively due to more

predictable conversion of pro-drug to active metabolite of prasugrel requiring a single cytochrome p450 metabolic step contrasted with Clopidogrel requiring two sequential steps. [50] Ticagrelor is a cyclopentyltriazolopyrimidines, which differs from Clopidogrel and prasugrel in that it is an active drug not requiring pro-drug conversion and binds to the platelet P2Y₁₂ receptor in a reversible manner. [51]

The concept of antiplatelet drug resistance or “hypo-responsiveness”

Although clinical trials have mostly deployed a “one-size-fits-all” strategy for antiplatelet medications, the pharmacodynamics, especially for aspirin and Clopidogrel, can vary substantially. Resistance to antiplatelet agents can be described in three ways: 1) Laboratory-based antiplatelet resistance, 2) High on-treatment platelet reactivity (HPR), and 3) Clinical antiplatelet resistance.

Before discussing the specifics, it is pertinent to briefly review platelet function testing. The historical gold standard for assessing antiplatelet resistance has been light transmission aggregometry (LTA), also known as turbidometric aggregometry. It is a measure of platelet-to-platelet aggregation. Agonists used include arachidonic acid and ADP for aspirin and ADP alone for Clopidogrel, prasugrel or ticagrelor. Similarly, impedance aggregometry using whole blood can be utilized to assess response to arachidonic acid and ADP. Both methods are time consuming and expensive; LTA also suffers from poor reproducibility.[52] Platelet function analyzer (PFA)-100 is another whole blood assay that assesses *in vitro* cessation of high shear blood flow by platelet plug. It is used mainly for monitoring aspirin effects. VerifyNow®, also known as Ultegra Rapid Platelet Function Assay (RPFA), is a simple, rapid, point-of-care test that uses arachidonic acid or propyl gallate to assess aspirin effects and ADP to assess P2Y₁₂ inhibitor effects. Vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) is a flow cytometric assay that assesses the level of activation of the platelet P2Y₁₂ receptor, and is specific for P2Y₁₂ inhibitor responsiveness. A platelet reactivity index (PRI) can be calculated, with higher percentage values corresponding to hypo-responsiveness to antiplatelet therapy; normal individuals (not on a P2Y₁₂ inhibitor) typically have values > 69%. [53] Although LTA and VASP-P show good correlation, LTA assesses multiple ADP pathways, while VASP-P only tests the ADP pathway relating to the P2Y₁₂ receptor. [54]

Laboratory-based antiplatelet resistance has traditionally been defined by percent change in platelet aggregation by LTA. Aspirin resistance is defined as 20% on-treatment platelet aggregation by LTA with 0.5 to 1.0 mg/mL arachidonic acid as the agonist.[55, 56] Clopidogrel resistance is defined as 10% change from pre- to on-treatment maximal aggregation by LTA with ADP stimulation. [57, 58]

Due to lack of reproducibility and inter-individual variability in baseline ADP-induced platelet aggregation,[59, 60] LTA has largely been replaced clinically by VerifyNow® and VASP assays. “On-treatment platelet reactivity” is a measure of the absolute level of platelet reactivity during treatment, while HPR is a categorical classification determined by on-treatment platelet reactivity at or above a threshold anticipated to represent clinically relevant hypo-responsiveness (i.e., associated with adverse clinical events).[60] Currently

recommended thresholds for HPR with Clopidogrel are listed in Table 1. [61-65] For the VerifyNow® aspirin assay, an Aspirin Reaction Unit (ARU) score of ≥ 550 units is typically considered as evidence of aspirin resistance. [66]

Clinical antiplatelet drug resistance refers to the development of a thrombotic event while taking antiplatelet medication due to ineffective or incomplete platelet inhibition. [52] Thus, the failure of aspirin to prevent an arterial thrombotic event can be considered clinically as evidence of aspirin resistance, and the failure of Clopidogrel to prevent an arterial thrombotic event is similarly considered Clopidogrel resistance. It should be noted that while true antiplatelet resistance is frequently encountered and will be discussed below, the most likely cause of antiplatelet resistance is, in fact, medication non-compliance.[67, 68] As well, thrombotic events may occur through pathways that are not platelet-mediated and therefore not modified by antiplatelet therapies.

Aspirin resistance in diabetes

The exact prevalence of aspirin resistance in patients with diabetes is unknown. Reasons include different performance characteristics of the various platelet function assays used, differences in aspirin dosing and characteristics of the patient populations studied. [69] Ertugrul and colleagues assessed laboratory-based aspirin resistance in 176 outpatients using impedance aggregometry. The overall prevalence was 43.5% in patients with diabetes and 26.9% in those without diabetes, with a modest positive correlation between Hb A1c levels and proportion of patients with resistance among the diabetes subset ($r=0.4$; $p<0.0001$). Criteria for resistance were also more common among participants treated with low dose aspirin (100 mg/day) compared with higher doses. [70] Similarly, using a PFA-100 system, the prevalence of laboratory-based aspirin resistance in patients with type 2 diabetes has been reported to range 20-25%. [71, 72] Using a VerifyNow® assay threshold of 550 ARUs, Kim and colleagues observed HPR in 9.8% in their cohort of 1,045 Korean patients with type 2 diabetes taking low dose aspirin. [73] Another study using the VerifyNow® assay showed comparable rates of HPR among patients with type 1 and type 2 diabetes (21.7% vs. 16.2%). [74]

In the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) registry of 8,582 patients undergoing percutaneous coronary intervention (PCI), 32.4% had diabetes mellitus. Aspirin was administered as either a non-enteric coated oral dose of ≥ 300 mg at least 6 hours before PCI, or as a chewed dose of 324 mg or intravenous dose of 250 mg or more ≥ 30 minutes before PCI. Overall HPR with aspirin (VerifyNow® ≥ 550 ARUs) was 5.6%. Diabetes mellitus, especially insulin-treated, was an independent risk factor for stent thrombosis and long-term mortality, but HPR with aspirin was not by itself predictive of stent thrombosis, MI or death. [62] On the other hand, Chen and colleagues observed HPR with aspirin (VerifyNow® ≥ 550 ARUs) in 27.4% of patients with established CAD. Diabetes mellitus was not a risk factor for HPR *per se*, but HPR with aspirin and diabetes mellitus were both independent predictors of the composite major adverse cardiovascular events (MACE) endpoint. [75] In summary, it appears that although the prevalence of HPR with aspirin in patients with type 2 diabetes is high, diabetes by itself does not confer a

higher risk for HPR with aspirin (as assessed by the VerifyNow® assay). Both HPR with aspirin and diabetes may be independent predictors of adverse long-term outcomes.

Strategies to overcome aspirin resistance in patients with diabetes include higher and more frequent dosing, although the latter appears to be more efficacious based on pharmacodynamic studies. This is partially based on the observation that patients with diabetes have higher platelet turnover. [39, 38] Addad and colleagues reported that aspirin 100 mg twice daily significantly reduced HPR compared with aspirin 100 mg once daily. [76] Spectre and colleagues further observed that 75 mg twice daily was more effective in decreasing aspirin resistance on aggregometric testing compared both, with 75mg and with 320 mg once daily. Although this was a small study, the twice daily regimen was more efficacious in patients with more reticulated platelets at baseline. [77] However, due to lack of dedicated outcomes studies, the twice daily regimen is not currently recommended by the guidelines. Current American Diabetes Association guidelines recommend aspirin in a dose of 75 to 162 mg daily in patients with diabetes with an increased risk of cardiovascular disease (for primary prevention), defined as men age >50 or women age >60 having at least 1 additional atherosclerotic vascular disease risk factor, or in those with established atherosclerotic vascular disease (for secondary prevention). [78] It should be noted that the primary prevention recommendation is not fully supported by available evidence from randomized controlled trials.

Clopidogrel resistance in diabetes

Clopidogrel is commonly utilized as part of a dual antiplatelet regimen along with aspirin in patients undergoing PCI or with recent ACS, and sometimes as monotherapy in patients with diabetes, CAD and aspirin intolerance. Subanalysis of data from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial indicates that Clopidogrel monotherapy may be superior to aspirin for reducing ischemic events in patients established atherothrombotic disease, with a greater absolute benefit toward cardiovascular event reduction in diabetic than non-diabetic patients.[79] Although Clopidogrel resistance has been studied more extensively than aspirin resistance, its prevalence estimates in patients with diabetes also varies based on assay, patient population and dose of Clopidogrel. [80] However, inter-individual variability in platelet response to Clopidogrel is now a well-established concept. Clopidogrel hypo-responsiveness is more prevalent in patients with diabetes, and is highest in insulin-treated patients. Angiolillo and colleagues observed that patients with diabetes undergoing PCI and receiving a single 300 mg loading dose of Clopidogrel had a significantly higher risk of being Clopidogrel non-responders when compared with patients without diabetes (38% vs. 8%, respectively). [81] A similar frequency of Clopidogrel hypo-responsiveness was observed in patients on maintenance therapy, with highest rates in patients with insulin-treated diabetes mellitus.[82] The Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS) trial screened 64 patients with type 2 diabetes on chronic dual antiplatelet therapy. Nearly 2/3rd of these patients had suboptimal platelet inhibition at baseline based on the VASP-P assay. [83]

In the ADAPT-DES registry, Clopidogrel was given as either a dose of 600 mg 6 hours before VerifyNow® testing, a dose of 300 mg 12 hours before VerifyNow® testing, or a

dose of 75 mg for at least 5 days before VerifyNow® testing. HPR with Clopidogrel was observed in 42.7% and 35.0% of patients when using platelet reactivity units (PRU) thresholds of 208 and 230, respectively. As discussed above, diabetes was an independent predictor of stent thrombosis and mortality at 1 year. In addition, Clopidogrel HPR defined as PRU ≥ 208 was associated with a significantly higher risk of stent thrombosis and MI at 1 year. Interestingly, the risk of stent thrombosis did not vary based on dose of Clopidogrel (75 mg, >75 - < 600 and ≥ 600 mg) used for loading. [62] In another study, Angiolillo and colleagues found that Clopidogrel-treated patients in the highest quartile of platelet reactivity with 20 µm/L ADP had the highest MACE event rates at 2 years. [84]

Given the high risk of adverse clinical events, strategies to mitigate Clopidogrel hypo-responsiveness have been extensively investigated. These have centered on a couple of key concepts. Firstly, Clopidogrel HPR in patients with diabetes can be attributed to both pharmacokinetic and pharmacodynamic issues. Recent work in patients with diabetes indicates that the former may be a larger issue than the latter – i.e., bioavailability may be a larger issue than impaired effectiveness of the active metabolite inhibiting platelet aggregation. [85, 86] To surmount the bioavailability issue, both higher and more frequent dosing have been evaluated. Secondly, given the large variability in Clopidogrel responsiveness, studies have investigated whether tailored therapy based on the results of dedicated platelet function assays would be helpful. However, barring the use of more potent or less pharmacodynamically variable antiplatelet medications, other strategies to mitigate HPR with Clopidogrel have not shown promising clinical results so far.

In the OPTIMUS trial mentioned earlier, the 40 patients identified as having HPR with Clopidogrel were randomized to continue Clopidogrel 75 mg daily or switched to 150 mg daily as maintenance therapy. The higher dose resulted in normalization of platelet inhibition in 40% of patients with baseline HPR. However, this was a small study and clinical outcomes data were not available. [83] In the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial, patients with acute coronary syndromes were randomized to receive standard Clopidogrel dosing (300 mg loading dose followed by 75 mg daily) versus higher-dose Clopidogrel (600 mg loading dose followed by 150 mg daily for 1 week and then 75 mg daily thereafter). There was no statistical difference in the primary outcome, 30-day MACE between the groups, in the overall trial population nor in the subset of 5,880 patients with diabetes.[87]

The utility of tailored Clopidogrel dosing guided by platelet function testing has been tested in large clinical trials. In the Gauging Responsiveness with a VerifyNow P2Y12 Assay—Impact on Thrombosis and Safety (GRAVITAS) trial, patients with documented Clopidogrel HPR with a single bolus dose of 600 mg of Clopidogrel (~1/2 of whom had prevalent diabetes) were randomized to daily Clopidogrel maintenance doses of 150 mg or 75mg. The higher daily maintenance dose resulted in a lower proportion of patients with HPR at 6 months (60% vs. 36%; $p<0.0001$). However, despite improved pharmacodynamic measures, after 6 months on study treatment, there was no statistical difference between the groups in the incidence of the primary trial endpoint of MACE events (2.3% vs. 2.3%; $p=0.97$). These overall trial results were similarly observed in the subset of patients with diabetes. [88]

Conversely, Bonello and colleagues randomized 162 patients undergoing PCI and evidence of Clopidogrel resistance on the VASP assay (PRI = 50%) with a single bolus dose of 600 mg Clopidogrel to a VASP-guided strategy or routine management. Escalating boluses of Clopidogrel were administered in the VASP-guided arm till PRI was < 50%. This strategy was effective in 86% of the patients, with bolus doses as high as 2,400 mg of Clopidogrel required to overcome Clopidogrel resistance.

There was a significant improvement in MACE rates at 1 month in the VASP-guided vs. routine management arms (0% vs. 10%, $p=0.007$). [89] Carreras and colleagues reported that patients with diabetes and carriers of the CYP2C19*2 allele required a 300 mg maintenance dose of Clopidogrel in order to achieve pharmacological equivalence to a 75 mg maintenance dose in non-diabetic wild-type carriers. [90] Thus, it is possible that higher loading and maintenance doses may be necessary to overcome HPR with Clopidogrel, but this needs to be assessed further in prospective studies, including in patients with diabetes.

Current guidelines for patients undergoing PCI provide a weak recommendation (class lib; i.e. “it is reasonable to consider”; Level of Evidence: C) for switching to prasugrel or ticagrelor if HPR with Clopidogrel is detected, and a similar recommendation for routine platelet function testing in selected high-risk patients treated with Clopidogrel. [91]

Newer antiplatelet medications in patients with diabetes

The pharmacodynamic challenges observed in patients treated with Clopidogrel, especially prevalent in the setting of diabetes, have been addressed to some extent with the development of novel antiplatelet medications with differentiated pharmacologic properties. The two currently available newer oral antiplatelet medications are prasugrel and ticagrelor. Like Clopidogrel, prasugrel is an irreversible P2Y₁₂ receptor inhibitor that requires metabolic conversion to its active metabolite following ingestion. However, in contrast to Clopidogrel, there is significantly less response variability and more potent P2Y₁₂ inhibition with prasugrel. [92] In patients with diabetes specifically, prasugrel was demonstrated to be more efficacious than high-dose Clopidogrel in attenuating HPR. In the OPTIMUS-3 trial, prasugrel administered as a 60 mg loading dose by 10 mg daily maintenance therapy resulted in greater platelet inhibition compared with Clopidogrel 600 mg loading dose followed by 150 mg maintenance therapy, as assessed by the VerifyNow® P2Y₁₂ assay. This effect was observed as early as 1 hour and sustained up to the end of the study (7 days). [93] Similarly, in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial of patients undergoing PCI, including 31% with diabetes, prasugrel 60 mg loading followed by 10 mg daily was superior to Clopidogrel 600 mg loading followed by 150 mg daily in inhibiting platelet aggregation during both the loading and maintenance phases. In the diabetes subset, there were no patients with residual HPR in the prasugrel arm. [92] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 trial compared prasugrel to Clopidogrel in patients presenting with an ACS undergoing PCI, and reported that prasugrel significantly reduced ischemic events compared with Clopidogrel, with a higher risk of bleeding. [94] The magnitude of benefit appeared to be greater in patients with diabetes for the primary

composite MACE outcome as compared with patients without diabetes (diabetes by treatment pinteraction=0.09), including a 40% reduction in the risk of MI ($p_{\text{interaction}}=0.02$), without a clear increase in bleeding. This effect was particularly pronounced in insulin-treated patients with diabetes, who had higher event rates overall, and thus a greater absolute benefit with prasugrel (NNT = 13 to prevent one ischemic event). [16]

Ticagrelor, a non-thienopyridine, does not require metabolic conversion *in vivo*. The PLATelet inhibition and patient Outcomes (PLATO) trial compared outcomes among patients randomized to treatment with ticagrelor versus Clopidogrel in ACS patients, and demonstrated a significant reduction in ischemic events with ticagrelor use. [95] In the subset of patients with diabetes (n=4,662), a comparable (but not greater) efficacy was observed and testing for heterogeneity of efficacy by diabetes was negative ($p_{\text{interaction}}=0.49$). Similarly, the magnitude of benefit in insulin-treated patients was similar to the overall cohort ($p_{\text{interaction}}=0.30$). [96] The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus Patients Intervention Study (THEMIS) trial is currently ongoing and seeks to compare ticagrelor to placebo for the prevention of adverse cardiovascular events in patients with diabetes and established coronary artery disease but without prior MI or stroke (NCT01991795).

There are limited randomized data comparing these two newer antiplatelet medications directly. A pharmacodynamic study compared the antiplatelet effects of a single loading dose of either ticagrelor 180 mg or prasugrel 60 mg in 100 patients with diabetes presenting with ACS. Platelet reactivity, assessed with the VASP assay, was lower in the ticagrelor arm compared with the prasugrel arm between 6 and 18 hours. HPR was numerically lower in the ticagrelor arm (6% vs. 16%). [97] However, in the absence of head-to-head assessment in clinical outcomes trials, there is no evidence for superiority of ticagrelor versus prasugrel; both are superior to Clopidogrel in population-based clinical studies, and pharmacodynamic data suggest more efficient antiplatelet effects among patients treated with Clopidogrel having HPR.

Role of other medications

Cilostazol is an older antiplatelet medication that selectively antagonizes the phosphodiesterase (PDE) 3 A enzyme. In addition, it also inhibits the uptake of adenosine, and has been shown to inhibit platelet aggregation. Most, if not all, of its actions are mediated by cyclic adenosine monophosphate (cAMP). [98] In the OPTIMUS-2 trial, patients with type 2 diabetes on dual antiplatelet therapy with aspirin and Clopidogrel were enrolled to receive either cilostazol 100 mg or placebo twice daily for 14 days and afterwards crossed-over treatment assignments for another 14 days. The addition of cilostazol to aspirin and Clopidogrel in this trial significantly lowered platelet aggregation. Its clinical use is limited by side effects such as headaches and GI disturbances; 20% discontinued cilostazol in OPTIMUS-2 due to side-effects. [99] Picotamide is a TX-A2 synthase and TX A2 receptor inhibitor that blocks TX A2 in pathways independent of aspirin. It could thus be a plausible alternative to aspirin in patients with true aspirin resistance or allergy. In a trial of patients with diabetes and peripheral artery disease,

picotamide reduced mortality compared with aspirin 320 mg daily.[100] It is currently not available in the United States.

The role of protease-activated receptor (PAR)-1 inhibitors in patients already on dual antiplatelet therapy is an area of active investigation. In the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA2P-TIMI 50) trial, vorapaxar use reduced CV events compared with placebo in patients with established atherosclerosis (the majority of whom were on dual antiplatelet therapy), but increased all bleeding, including intracranial hemorrhage. The overall efficacy of vorapaxar appeared similar among patients with and without diabetes. [101] It remains unknown whether there may be a role for PAR-1 inhibition in patients with high on-treatment platelet reactivity on Clopidogrel. Other TX A2 inhibitors such as EV-077 and terutroban sodium are also being investigated. [102]

Conclusions

Patients with diabetes mellitus have a high residual risk of recurrent ischemic events despite contemporary evidence-based treatment with antiplatelet medications. Antiplatelet medication resistance or on-treatment HPR appears to be an important contributor to this phenomenon. Clopidogrel hypo-responsiveness is especially prevalent in patients with diabetes. The use of novel antiplatelet medications such as prasugrel and ticagrelor appears to significantly improve HPR with Clopidogrel, observations buttressed by superiority of each demonstrated versus Clopidogrel in randomized clinical outcomes trials. Future studies of novel antiplatelet medications should specifically assess response in this high-risk subset.

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Figure 1. Mechanisms causing platelet derangements in diabetes mellitus

ADP indicates adenosine diphosphate; ET-1, endothelin-1; Gp, glycoprotein; HDL, high-density lipoprotein; IRS, insulin receptor substrate; LDL, low-density lipoprotein; NFκB, nuclear factor-κβ; NO, nitric oxide; PKC, Protein kinase C; ROS, reactive oxygen species; TG, triglycerides; Tx, thromboxane; VCAM-1, vascular cell adhesion molecule-1; VLDL, very-low-density lipoprotein

Table 1
Platelet reactivity cutoffs associated with ischemic events with clopidogrel [61]

Assay	Threshold
VerifyNow PRU assay, PRU	>208 [62]
ADP-induced aggregation, AU	> 46 [63]
ADP-induced platelet-fibrin clot strength, mm	> 47 [64]
VASP-PRI	50% [65]